ORIGINAL ARTICLE

Biochemical evidence of myocardial fibrosis in veteran endurance athletes

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Background: Studies on exercise-induced left ventricular hypertrophy (LVH) in veteran athletes suggest the presence of abnormal diastolic filling and incomplete regression of LVH on cessation of exercise.
Hypothesis: Myocardial fibrosis occurs in exercise induced LVH in veteran athletes.
Aim: To document non-invasively the presence of fibrosis in veteran athletes
Design: Prospective case–control study.
Setting: City centre district general hospital.
Participants: 45 normotensive elite veteran athletes and 45 normal sedentary subjects.
Interventions: Echocardiographic assessment was made of LV mass, LV systolic and LV diastolic function. Plasma carboxyterminal propeptide of collagen type I (PICP), carboxyterminal telopeptide of collagen type I (CITP) and tissue inhibitor of matrix metalloproteinase type I (TIMP-1) were measured as markers of collagen synthesis, degradation and inhibition of degradation, respectively.
Results: Veteran athletes had significant elevation in LV dimensions and calculated LV mass index (LVMI). Diastolic and systolic function was normal. Plasma PICP (259 vs 166 μg/l, $p<0.001$), CITP (5.4 vs 2.9 μg/l, $p<0.001$) and TIMP-1 (350 vs 253 ng/ml, $p=0.01$) were elevated in the cohort of athletes. There was a further elevation of TIMP-1 in athletes with echocardiographic LVH, defined as an LVMI >130 g/m^2 (417 vs 266 ng/ml, $p=0.02$).
Conclusion: There is biochemical evidence of disruption of the collagen equilibrium favouring fibrosis in veteran athletes with LVH. This may suggest that fibrosis occurs as part of the hypertrophic process in veteran athletes.

Chronic high-intensity exercise results in structural cardiac changes in the human heart. Henschen[1] first described this at the end of the nineteenth century. The changes are characterised by an increase in left ventricular chamber dimensions and an increase in left ventricular wall thickness.[2] This is traditionally thought to be non-pathological, as the hypertrophy regresses on cessation of exercise,[3 4] it is thought to consist mostly of myocyte hypertrophy, and Doppler indices of diastolic filling are on the whole within age-matched limits.[5 6]

This situation may, however, be different in veteran athletes. The limited data available for this cohort suggest that diastolic function is abnormal, and, more importantly, that incomplete regression of LVH occurs on cessation of exercise.[7 8] Our hypothesis was that these findings could be explained by the presence of co-existent fibrosis.

Fibrosis occurring in the context of LVH has important pathological consequences,[9] and therefore the demonstration of fibrosis present in exercise-induced LVH would be a key finding in our understanding of the clinical significance and potential long-term consequences of LVH.

The biochemical assessment of fibrosis using collagen markers represents a practical, validated and non-invasive method for the assessment of fibrosis in this cohort of veteran athletes. The clinical utility of this technique in the context of left ventricular hypertrophy has been demonstrated by our group,[10] and also, most notably, by Diez *et al*.[11–13]

The aim of this study was to show, using biochemical markers, the presence of fibrosis in exercise-induced LVH in a cohort of veteran athletes.

METHODS

Subjects

We enrolled a cohort of veteran athletes who were active members of the Scottish Veteran Harriers club. We aimed to recruit a cohort of elite veteran athletes who continued to exercise and compete at a high level. The inclusion criteria were (1) male and aged >45 years; (2) subjects must have been running for more than 10 years at a competitive level; and (3) subjects must be currently running >30 miles/week and regularly competing in elite veteran endurance events.

Exclusion criteria were conditions that result in (1) LVH—namely hypertension and aortic stenosis; (2) conditions that result in fibrosis, thus preventing spurious elevation in collagen markers of synthesis and degradation. These conditions included renal impairment (serum creatinine>130 mmol), history or symptoms consistent with coronary artery disease, malignancy, pulmonary fibrosis, connective tissue disorders, significant hepatic dysfunction, left ventricular systolic dysfunction (ejection fraction <50% on echo) and smoking-related airways disease.

A cohort of sedentary normal subjects was recruited via a local advertising campaign. Ethical approval was obtained from the local ethics committee. All subjects received a full written and verbal explanation of the investigations involved and the aims of the study. Written consent was obtained in all cases before any investigations were carried out.

Study conditions

Patients were studied at a standard time in the morning on one study day. A full history and clinical examination was made to identify exclusion criteria and suitability for the study. Blood

Abbreviations: CITP, carboxyterminal telopeptide of collagen type I; IVSd-1, interventricular septal thickness in diastole; LPWd, left posterior wall thickness in diastole; LV, left ventricular; LVH, left ventricular hypertrophy; LVIDd, left ventricular internal dimension in diastole; LVMI, left ventricular mass index; PICP, plasma carboxyterminal propeptide of collagen type I; RWT, relative wall thickness; TIMP-1, tissue inhibitor of matrix metalloproteinase type I

Table 1 Baseline criteria

	Athletes	Normal subjects	p Value
Number	45	45	NS
Systolic BP (mm Hg)	129 (2.4)	129 (2.6)	NS
Diastolic BP (mm Hg)	77 (1.2)	77 (2)	NS
Duration of training, years (range)	20 (1.9) (2–50)	0	<0.01
Weekly training, km (range)	48 (3.84) (16–112)	0	<0.01
BSA	1.88 (0.02)	1.83 (0.04)	NS
Age, years (range)	52 (1.7) (45–75)	52 (31–74)	NS

BP, blood pressure; BSA, body surface area; NS, not significant.
Values are given as mean (SEM) (ranges).

pressure was recorded with a mercury sphygmomanometer in the supine position and an average of three readings was taken.

Echocardiographic study

Patients were studied using a Vingmed CFM800 sonos or a Vingmed System 5 echo machine (Vingmed Sound A/S, Horten, Norway). Examinations were made in a darkened room in the standard left lateral position. Echo measurements were taken in the standard parasternal and apical positions. M-mode measurement was taken in a perpendicular parasternal long-axis view, with the cursor through the tips of the mitral valve leaflets. Measurements were taken according to the guidelines laid down by the American Society of Echocardiography.[14] Left ventricular mass was calculated using the formula validated by Devereux and Reichek[15] and indexed for body surface area. An average of at least three measurements was taken and images were stored on a super VHS videotape and on a digital archiving facility (Vingmed EchoPac). Ventricular function was assessed via calculation of fractional shortening and left ventricular ejection fraction from a left ventricular m-mode. Measurement of early:atrial (E:A) ratio was made in the apical view, with a cursor at the mitral valve inflow. An average of three measurements was taken at end expiration, and images were stored on a digital archive.

Standard assessment of valvular function was made.

A single observer (MML) made all measurements. Using digital archiving images, intraobserver variability was tested in a blinded fashion. Intraobserver variability was 3.5% and 9% for E:A ratio and calculated left ventricular mass index (LVMI), respectively.

Biochemical measurements

Routine biochemical measurements were taken and analysed in the standard way.

All samples were taken at a standard time after 30 min in the supine position. Samples were immediately centrifuged at 3000 rpm for 7 min and the plasma layer removed. The separated plasma was divided into three equal aliquots and frozen at −80°C. Samples were not thawed and refrozen.

Plasma tissue inhibitor of matrix metalloproteinase type I (TIMP-1) was measured as a marker of inhibition of collagen degradation. Plasma carboxyterminal telopeptide of collagen type I (CITP) was measured as a marker of collagen degradation and plasma carboxyterminal propeptide of collagen type I (PICP) as a marker of collagen synthesis.

Plasma TIMP-1 was measured using a commercially available two-site enzyme-linked immunosorbent assay specific for TIMP-1 (Amersham Pharmaceuticals, Buckinghamshire, UK). This technique is a modified version of that described by Plumpton *et al*.[16] All samples were analysed in duplicate and intra-assay variability was 4.5%.

Plasma CITP was measured by radioimmunoassay using a polyclonal antibody directed against CITP.[17] All samples were run in duplicate, with the intra-assay variability calculated as 4.3%.

Plasma PICP was measured using a radioimmunoassay. Samples were run in duplicate, with the intra-assay variability calculated as 4.2%.

ECG

All patients received a standard 12-lead ECG with a paper speed of 25 mm/s. This was recorded in the supine position on the same study day as the other recordings. ECGs were analysed for the presence of LVH and ST-T changes using standard criteria.[18] Additionally, the presence of atrial abnormalities was assessed using predefined criteria.[19] All ECGs were analysed by a single observer (ML).

Statistical analysis

The distribution of the collagen markers was tested for normality using the Anderson–Darling test. All markers were not normally distributed. Therefore, results were log transformed before analysis. Results are presented in the non-logarithmic format. All continuous variables were analysed using unpaired Student's t test. Non-continuous variables were analysed using a χ^2 test.

RESULTS

In all, 45 athletes (5 athletes were excluded before recruitment and analysis, owing to hypertension (1 subject), renal impairment (1 subject) and poor echo views (3 subjects)) and a matched population of 50 normal subjects were recruited. Four normal subjects were excluded before recruitment and analysis (2 subjects with hypertension and 2 with poor echo views).

Baseline criteria

The two groups were well matched for age, blood pressure and body surface area (table 1)

Table 2 ECG findings in athletes and normal volunteers

ECG finding	Athletes (%)	Normal subjects (%)	p Value
LVH	36	0	<0.001
ST-T changes	11	0	<0.01
Atrial abnormalities	9	9	NS

LVH, left ventricular hypertrophy; NS, not significant.

Table 3 Echo parameters in athletes and normal volunteers

Parameter	Athletes	Normal subjects	p Value
IVSd, cm (range)	1.2 (0.03) (0.8–1.6)	0.9 (0.03) (0.6–1.2)	<0.01
LVIDd, cm (range)	5.2 (0.06) (4.2–6.1)	4.8 (0.07) (3.6–5.6)	<0.001
LPWd, cm (range)	1.1 (0.02 (0.6–1.3)	0.9 (0.02) (0.6–1.3)	0.04
RWT, cm (range)	0.4 (0.01) (0.3–0.6)	0.4 (0.01) (0.2–0.5)	0.002
LVMI, g/m^2	141 (5)	97 (3)	<0.001
E:A ratio	1.2 (0.07)	1.1 (0.03)	NS
Max A wave (m/s)	0.6 (0.02)	0.7 (0.03)	NS
Max E wave vel(m/s)	0.7 (0.03)	0.7 (0.03)	NS

IVSd, interventricular septal thickness in diastole; LPWd, left posterior wall thickness in diastole; LV, left ventricular; LVH, left ventricular hypertrophy; LVIDd, left ventricular internal dimension in diastole; NS, not significant; PICP, plasma carboxyterminal propeptide of collagen type I; RWT, relative wall thickness.
Values are given as mean (SEM) (ranges).

ECG findings

Using the above criteria, 36% of athletes and no normal subjects were found to have LVH (p<0.001). Also, 11% of athletes and no normal subjects had ST-T abnormalities (p<0.01). There was no difference in the incidence of atrial abnormalities. There was no relationship between any of the collagen markers and ECG findings (table 2)

Echocardiography

The cohort of athletes, compared with controls, had a significant increase in interventricular septal thickness in diastole (IVSd; 1.17 vs 0.9 cm, p<0.01), left posterior wall thickness in diastole (LPWd; 1.1 vs 0.91 cm, p = 0.04), left ventricular internal dimension in diastole (LVIDd 5.2 vs 4.8 cm, p<0.001) and left ventricular mass index (LVMI; 141 vs 97 g/m^2, p<0.001). There was no difference in indices of diastolic filling. In all, 57% of the athletes had an LVMI >130 g/m^2, showing a high incidence of exercise-induced LVH. Relative wall thickness (RWT) was significantly elevated among athletes compared with controls (0.42 vs 0.37 cm, p = 0.002), suggesting that the hypertrophy present was concentric in nature (table 3).

Collagen markers

Tissue inhibitor of matrix metalloproteinase type I

Plasma TIMP-1 was significantly elevated in the cohort of athletes compared with the normal control group (350 vs 253 ηg/ml, p<0.01, 95% CI 20 to 174). When the cohort of athletes was dichotomised depending on the presence or absence of exercised-induced LVH (defined as LVMI >130 g/m^2),[20] the athletes with LVH were found to have significantly higher plasma TIMP-1 levels (417 vs 266 ng/ml, p = 0.01, 95% CI 27 to 276; fig 1). In fact, the athletes without LVH had plasma TIMP-1 levels comparable to those of the cohort of normal subjects (266 vs 253 ng/ml, p = NS, 95% CI –61 to 34). No relationship was seen with duration or intensity of training.

The cohort of athletes with exercise-induced LVH were then further characterised to exclude confounding factors, which could explain the elevation in TIMP-1. Table 4 shows that there is no significant difference in any of the baseline criteria between the two groups. Therefore, the elevation in TIMP-1 seems to reflect a genuine increase in inhibition of collagen degradation in athletes with exercise-induced LVH.

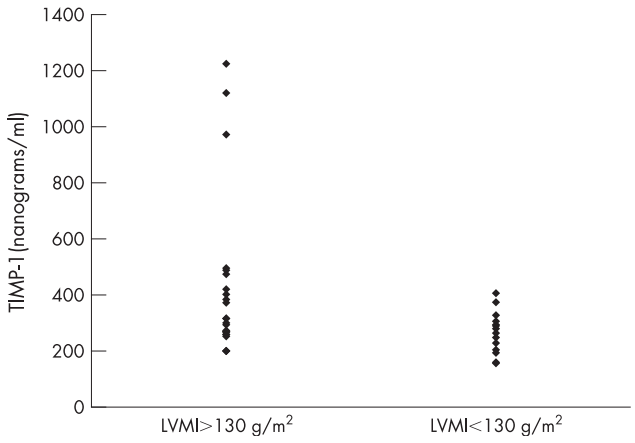

Figure 1 Data points show plasma tissue inhibitor of matrix metalloproteinase type I concentrations (ng/ml) in athletes with left ventricular mass index (LVMI) >130 g/m^2 and in athletes with LVMI <130 g/m^2.

Carboxyterminal telopeptide of collagen type I

Plasma CITP levels were significantly elevated in the cohort of athletes compared with the normal volunteers (5.4 vs 2.9 μg/l, p<0.001, 95% CI 1.9 to 3.1, fig 2). This elevation was shown in athletes with and in those without LVH. No relationship was shown between CITP and LV dimensions, LV mass, and duration or intensity of exercise.

Plasma carboxyterminal propeptide of collagen type I

Plasma PICP levels were also elevated within the cohort of athletes compared with normal volunteers (259 vs 166 μg/l, p<0.001), 95% CI 60 to 126; fig 3). This elevation was shown in athletes with and in those without LVH. Again, no relationship was shown between PICP and LV dimensions, LV mass, and duration or intensity of exercise.

DISCUSSION

Exercise-induced LVH is widely thought to be a benign physiological process. However, in the absence of prospective controlled studies, this cannot be certain. There is evidence available that should make us re-examine conventional thinking. Firstly, the fact that exercise-induced LVH regresses on cessation of exercise does not confirm its physiological basis. All pathological forms of LVH—namely, hypertensive heart disease and LVH in the context of aortic stenosis—regress on removal of the pathological stimulus, as does exercise-induced LVH. Secondly, follow-up studies purporting to confirm that athletes have increased life expectancy are flawed, as these studies have not been controlled for major cardiovascular risks such as smoking.[21] Finally, postmortem studies have revealed an incidence of 18% of idiopathic LVH in sudden cardiac death in athletes.[22] Clearly, these limited data cannot confirm a causative role of LVH; however, these should raise some concern.

The issue of the possible pathological role of exercise-induced LVH in veteran athletes is even less well defined. The studies

Table 4 Athletes with left ventricular mass index (LVMI) >130 g/m^2 vs athletes with LVMI <130 g/m^2

Parameter	LVMI>130 g/m^2	LVMI<130 g/m^2	p Value
Age (years)	52 (2.5)	53 (3)	NS
BSA	1.9 (0.02)	1.8 (0.05)	NS
Systolic BP (mm Hg)	129 (3)	129 (5)	NS
Diastolic BP (mm Hg)	77 (1)	76 (3)	NS
Max E wave velocity (m/s)	0.75 (0.04)	0.73 (0.03)	NS
E:A ratio	1.4 (0.08)	1.3 (0.13)	NS
TIMP-1 (ng/ml)	417 (57)	266 (20)	0.01
CITP (μg/l)	5.6 (0.4)	5.2 (0.3)	NS
PICP (μg/l)	258 (19)	273 (23)	NS
Duration of training (years)	19 (2.7)	21 (3)	NS
Weekly training (miles)	26 (2.7)	37 (4)	0.06

BP, blood pressure; BSA, body surface area; CITP, carboxyterminal telopeptide of collagen type I; LVMI, left ventricular mass index; NS, not significant; PICP, plasma carboxyterminal propeptide of collagen type I; TIMP-1, tissue inhibitor of matrix metalloproteinase type I.
Values are given as mean (SEM).

available reveal some concerning findings—namely, that middle-aged athletes are more prone to developing ECG abnormalities, prominent hypertrophy and may have slightly depressed LV function.[8] In addition, diastolic function may be abnormal, and regression of LVH after 2 years of cessation of exercise may be incomplete.[7]

It was this finding of incomplete regression of LVH in veteran athletes that was the stimulus to our study. If regression was incomplete, then this may reflect pathological abnormalities—namely, that, in addition to the accepted myocyte hypertrophy, there may in fact be a degree of interstitial fibrosis. Interstitial fibrosis occurring in the context of LVH is an important pathological entity resulting in the development of diastolic dysfunction and acting as a substrate for ventricular arrhythmias.[23] Therefore, the demonstration of fibrosis would be an important finding in allowing us to understand the clinical significance and consequences of exercise-induced LVH.

Biochemical assessment of the collagen equilibrium is now possible. PICP, which is cleaved on incorporation of procollagen type I into the collagen helix, has been shown to be a non-invasive measure of fibrogenesis.[24 25] CITP, which is cleaved when collagen type I is degraded, has been shown to be a measure of collagen degradation.[17 26] Finally, TIMP-1, which is a naturally occurring specific inhibitor of matrix metalloproteinases, which are the rate-limiting step in collagen degradation, has been shown to be a measure of inhibition of collagen degradation.[27] Therefore, by measurement of PICP, CITP and TIMP-1, we achieved an accurate biochemical assessment of both sides of the collagen equilibrium. The clinical utility of biochemical markers of fibrosis in the context of LVH has been previously demonstrated by our group.[10] These markers are not specific to the myocardium. Hence, care was taken to exclude individuals with conditions that may result in fibrosis through other means.

Care was taken to enrol a cohort of elite athletes who would have exercise-induced cardiovascular changes. This was achieved using strict inclusion criteria. All echo parameters of LV mass were significantly increased, and 57% of our cohort had an LVMI >130 g/m^2.

Our results demonstrate that in elite veteran athletes there is biochemical evidence of disruption of the collagen equilibrium in comparison with a matched cohort of sedentary control subjects. Taking the cohort of athletes as a whole, we have shown a significant increase in collagen synthesis as assessed by an elevation in PICP, an increase in collagen degradation as assessed by an elevation in CITP and an increase in inhibition of degradation as assessed by an elevation in TIMP-1. Of more significance is the finding that athletes with echo evidence of exercise-induced LVH (LVMI>130 g/m^2) had a further statistically significant elevation in TIMP-1. Indeed, TIMP-1 was elevated only in athletes with LVH; the remaining athletes had TIMP-1 levels comparable to normals. Therefore, there only

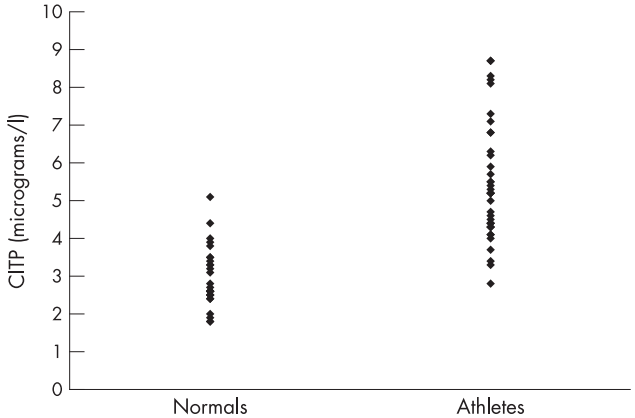

Figure 2 Data points show plasma carboxyterminal telopeptide of collagen type I concentrations (μg/l) in athletes and normal volunteers (normals).

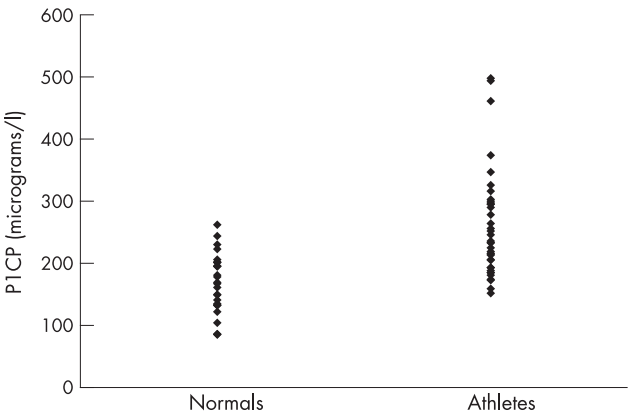

Figure 3 Data points show plasma carboxyterminal propeptide of collagen type I (PICP) concentrations (μg/l) in athletes and normal volunteers (normals).

What is already known

- High-intensity exercise results in cardiac changes including left ventricular hypertrophy (LVH).
- Exercise-induced LVH is currently thought to be a benign process.
- Fibrosis occurring as part of LVH has important pathological consequences.

What this study adds

Fibrosis may occur as part of the exercise-induced hypertrophic process in veteran athletes.

appears to be an elevated inhibition of degradation (TIMP-1) among athletes with LVH. This disruption of the collagen equilibrium among athletes with LVH, characterised by inhibition of collagen degradation, would favour the development of fibrosis. This contrasts with P1CP and CITP, which were elevated among the cohort of athletes irrespective of the presence of LVH.

These findings may suggest that increments in collagen synthesis and degradation occur at an early stage in the development of exercise-induced cardiovascular adaptation, whereas inhibition of collagen degradation occurs only in more advanced stages of cardiovascular adaptation associated with established exercise-induced LVH. Within the setting of exercise-induced LVH, increments in inhibition of collagen degradation may favour the development of fibrosis. The finding of elevated TIMP-1 among athletes with LVH cannot be explained by confounding factors and represents a genuine elevation.

It should be noted that the cohort of veteran athletes studied did not show evidence of diastolic dysfunction, which might be expected in the context of myocardial fibrosis. There are several possible explanations for this. Diastolic dysfunction is a complex process, which has been best described in the context of hypertensive LVH. However, the factors involved in the development of fibrosis in hypertensive heart disease are clearly different from those important in exercise-induced LVH—namely, in hypertensive heart disease, there are chronic elevations in the effector hormones of the renin angiotensin system, which are central to the development of fibrosis and independent of myocyte hypertrophy.[28] Fibrosis, if present in exercise induced LVH, is likely to be mediated by different factors and may relate to the chronic loading of regular high-intensity exercise. In addition, due to the complex cardiovascular adaptive changes that occur in exercise-induced LVH, the development of diastolic dysfunction secondary to fibrosis may occur much later in this process than is seen in hypertensive heart disease. Therefore, the absence of diastolic dysfunction in this cohort of athletes does not imply the absence of fibrosis.

Another possible explanation for our findings would be that the changes in the collagen equilibrium shown merely reflect remodelling associated with increments in LV mass. However, if this were the case, then one would expect a direct correlation between increasing LV mass and increments in PICP, CITP and TIMP-1. This is not seen. There are no correlations with markers of the collagen equilibrium and any echo assessment of LV mass. Furthermore, TIMP-1 levels are elevated only in the presence of documented LVH. Therefore, we feel this explanation can be discounted.

The major limitation of this study is that we rely on non-invasive biochemical markers of fibrosis in an attempt to show fibrosis and do not have definitive pathological evidence. However, the assays used are robust, our laboratory reproducibility is satisfactory and our cohort well characterised. Furthermore, routine myocardial biopsy in this population could not be justified.

In conclusion, our results suggest that there is biochemical evidence of disruption of the collagen equilibrium favouring fibrosis in veteran athletes with LVH. This may suggest that fibrosis occurs as part of the hypertrophic process of exercise-induced LVH in veteran athletes. This would provide a possible explanation of incomplete regression of LVH in this cohort and may suggest that this process is pathological.

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Competing interests: None declared.

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EDITORIAL BOARD MEMBER

Per Renström

Per Renström was born in 1942. He was certified as a medical doctor at Göteborg University in Sweden in 1972. He finished his residency in 1977. In 1981, he gained a PhD, the research topic being below-knee amputees. Until 1988, he worked at the Department of Orthopaedics at Sahlgren University Hospital in Göteborg. In 1988, he and his family relocated to the University of Vermont in Burlington, where he had a full professorship in orthopaedics and sports medicine. In 1997, he returned to Sweden as professor of sports medicine at the Karolinska Institutet.

Since 1967 Per has been married to Lena, who has a PhD in science education and is now working at the Education University of Stockholm.

Per has been very active in sports medicine research. His research topics include biomechanical and clinical studies, particularly of knee and ankle ligaments, Achilles tendons, and amputation and prosthetics. He is author of over 400 publications, including over 200 full scientific papers, of which 125 are in peer reviewed journals.

The book *Injuries in sports*, authored by Per together with Lars Peterson, is the most widely available sports injury book in the world, and a new edition came out in November 2000. Per also edited two volumes of the International Olympic Committee (IOC) *Encyclopedia series on sports medicine*. He has published or edited 16 books and written 42 book chapters.

With his research group, Per has twice received the Albert Trillat Investigator Award (1993 and 1997) from the International Society of the Knee and the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS), and twice the O'Donoghue Award (1996 and 1998) from the American Orthopedic Society of Sports Medicine (AOSSM). He has also received the Kappa Delta Award (1994) for outstanding orthopaedic research from the American Academy of Orthopedic Surgeons and Orthopedic Research Society, which is the most prestigious research award in orthopaedics. He received the Beijersdorf Research award from GOTS (German Orthopedic and Trauma Society) in 2000.

Per has been and is very active in sports medicine organisations. He has been secretary, vice president and president of the Swedish Society of Sports Medicine, where he now is an honorary member. He was appointed chairman of the Swedish Sport Research Council by the Swedish Government in 2000. He was vice president of the International Sports Medicine Federation (FIMS) in 1990–1998. He is a member of the Medical Commission of the IOC and the IOC Publication Advisory Subcommission. He is a founding member of the IOC Olympic Academy of Sport Sciences.

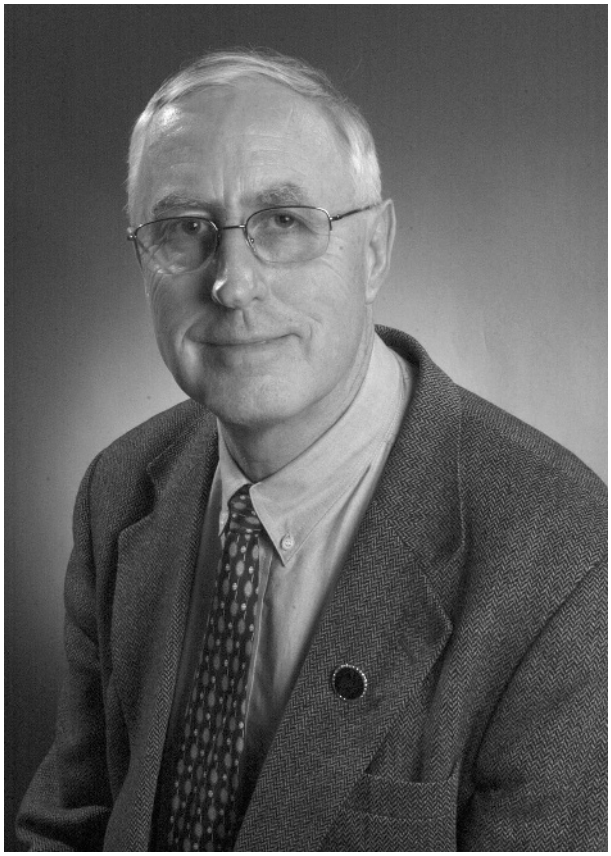

Figure 1 Per Renström.

In 2003–2005, Per was president of ISAKOS, which is a world wide society for all active in orthopaedic sports medicine, arthroscopy and knee surgery. He is a member of the Medical Commission of the International Tennis Federation (ITF), former president of the International Society of Medicine and Science in Tennis, medical director of the ATP, and a former physician to the Swedish Davis Cup team.